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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 11/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,931	MAHLER ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-34,37-41,43-46 and 48-54* is/are pending in the application.

4a) Of the above claim(s) *24-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,37-41,43-46 and 48-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received September 20, 2006 are acknowledged.

Claims 1-23, 35, 36, 42, and 47 have been canceled.
Claim 33 has been amended.
Claims 53 and 54 have been added.
Claims 24-34, 37-41, 43-46, and 48-54 are pending.
Claims 24-32 stand withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the restriction requirement mailed June 7, 2004.

Claims 33, 34, 37-41, 43-46 and 48-54 are under examination in this office action as they read on methods of treating IgE-mediated allergic disorders by administering allergen derivatives.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. The rejection of claims 33, 34, 37-41, and 43-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because tree pollens are not members of the genus of grass pollens has been withdrawn in view of applicant's claim amendments received 9/20/06.

Specifically, applicant has removed the recitation of grass pollen from all claims presently under examination.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 33, 34, 37-41, 43-46 and 48-52 stand rejected and new claims 53 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The office action mailed June 20, 2006 states:

> Independent claim 33 recites that the administered allergen derivative induces IgE-blocking antibodies and that specific IgE binding to the administered derivative is 50% or less as compared with IgE binding to the naturally occurring allergen. The specification teaches on page 4 that the administered allergen derivative is to have less than 50% of the allergenic activity of the wildtype allergen from which it is derived, and defines allergenic activity as the capacity to induce an IgE response upon administration to a test animal. The specification further teaches on page 4 that the basophil histamine release assay is a preferred *in vitro* test for determining allergenic activity. The specification does not appear to support the limitation that specific IgE binding to the allergen derivative is 50% or less as compared to the wildtype allergen since the binding to preexisting IgE antibodies and the ability to elicit new IgE antibody production are distinct properties. For example, Valenta et al. teach an allergen derivative that binds preexisting IgE comparable to the wildtype allergen yet does not induce histamine release from basophils (WO 99/16467, see entire document, particularly lines 22-23 of page 10, the paragraph spanning pages 11 and 12, and page 13). Note that all other claims under examination depend directly or indirectly from claim 33, and that none of these claims further limit the claimed invention such that the new matter is excluded.
>
> Dependent claim 47 recites that grass pollen allergens are to be selected from the group consisting of alder, hazel, and birch, while dependent claims 46, 51 and 52 limit the grass pollen allergen to Bet v 1, the major allergen found in birch pollen. Tree pollen allergens and grass pollen allergens are generally recognized in the art as being structurally distinct from one another, as evidenced by chapters 10 and 11 of Lockey et al. (Allergens and Allergen Immunotherapy, third edition, 2004, pages 165-205, see entire document), and patients known to suffer from grass pollen allergies do not have antibodies that also bind the birch pollen allergen Bet v 1 as taught by Valenta et al. (ibid, see particularly the paragraph spanning pages 17 and 18). Further, the paragraph spanning pages 2 and 3 of the specification teaches that derivatives of allergenic proteins can be made from a non-limiting list of allergens that includes Bet v 1 and grass pollen allergens, but this paragraph does not teach that Bet v 1 is a grass pollen allergen. As such applicant's definition of alder, hazel, birch, and the specific allergen Bet v 1 as members of the genus of grass pollen allergens via the claims is new matter.

Applicant's arguments filed September 20, 2006 have been fully considered but they are not persuasive. Applicant argues that the examiner has too narrowly construed the teachings of the specification concerning the phrase "allergenic activity" to be limited to the capacity to generate production of new IgE antibodies.

Applicant's argument is not persuasive. On page 2 the specification states:

> The invention therefore relates to the use of a derivative of an allergenic protein which derivative has a reduced allergenic activity compared with an allergenic protein from which it is derived for the preparation of a medicament for the treatment or prevention of an allergic disorder wherein the medicament is administered to a patient two to six times with the proviso that the time intervals between the administrations are at least 14 days.

On page 4 the specification states:

> According to the invention the allergenic activity of a sample is determined by determining the IgE antibodies which are induced in a test animal upon application of the sample.

The Merriam-Webster OnLine dictionary defines "induce" as "to call forth or bring about by influence or stimulation, effect, cause, to cause the formation of". As such, the specification defines allergenic activity as causing the production of new IgE antibodies. It was known in the art that the ability of a polypeptide to cause new IgE antibodies to be produced and the ability of a peptide to be bound by preexisting IgE antibodies are separable functional properties (WO 99/16467, of record). Since these two functional properties are not identical and are not necessarily simultaneously present, applicant's recitation that a derivative binds IgE to a lesser extent than the wild type allergen comprises new matter since derivatives are taught as possessing reduced allergenic activity and allergenic activity is not defined in relation to IgE binding levels. Thus the rejection is maintained.

Note that the new matter rejection concerning the recitation of tree pollen allergens as grass pollen allergens has been withdrawn in view of applicant's removal of the phrase "grass pollen" from independent claim 33.

6. Claims 33, 34, 37-41, 43-46 and 48-52 stand rejected and new claims 53 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record.

The office action mailed June 20, 2006 states:

Applicant has claimed a method of treating or preventing IgE-mediated allergic disorders by repeatedly administering derivatives of a known allergen. The specification teaches many IgE-mediated disorders on page 1, and teaches that the IgE antibodies that are responsible for mediating these conditions are allergen specific. The claim recites that the administered agent is a modified grass pollen allergen, yet the claim preamble does not limit the IgE-mediated disorders to those that involve only grass-pollen allergen specific IgE antibodies. As such, it does not appear that applicant's method would treat or prevent all IgE-mediated allergic disorders since the IgE antibodies responsible for such disorders are often specific for allergens other than grass pollen, such as insect proteins and drugs (Ipsen et al. of record, see entire document, particularly paragraph 3).

Further, while the specification teaches methods for the treatment or prevention of allergic disorders (see particularly page 2 of the specification), the specification does not appear to define the term prevent. Allergic reactions occur subsequent to allergen reexposure, and as such therapy needs to be initiated prior to the development of an allergen specific IgE response to prevent the occurrence of an IgE mediated disorder. The development of an allergen specific IgE response is due to the complex interplay of environmental and genetic factors, and therefore it is not predictable who will or will not develop an allergic response to a given allergen (chapter 2 of Lockey et al. in Allergens and Allergen Immunotherapy, third edition, 2004, pages 37-50, see entire document particularly pages 42-46, Figure 2, and the salient points section spanning pages 47 and 48). The claims recite that the allergen derivative is to be administered to a patient in need thereof, but as discussed above it is unpredictable who will or will not develop an IgE-mediated disorder specific for a given allergen. As such the only identifiable patients in need of treatment are those already known to suffer from allergies specific for a given allergen. These patients currently have an ongoing IgE-mediated immune response directed to the specific allergen, and as such the IgE-mediated reaction cannot be prevented because it has already occurred.

Applicant's claimed method is also broad in that the independent claim recites a method wherein an agent is administered to a patient, wherein the agent is known to comprise the functional properties of inducing an IgE-blocking antibody response and having reduced specific IgE binding as compared to the naturally occurring allergen due to its selection via a recited screening protocol. The administered agent is a derivative of a naturally occurring allergen, and in the paragraph spanning pages 2 and 3, the specification teaches that derivatives of an allergen can be fragments, oligomers, and chemically modified forms of naturally occurring allergens as well as molecules obtained by site directed mutagenesis of an allergen protein.

Polypeptide derivatives of allergens are known in the art, and applicant has provided examples of three derivatives of Bet v 1, namely a trimer of Bet v 1, the polypeptide consisting of amino acids 1-73 of Bet v 1, and the polypeptide consisting of amino acids 74-159 of Bet v 1 to support the claimed invention. Claim 52 limits the invention in that the derivative used for immunotherapy is a trimer of Bet v 1, and this claim depends from claim 33, which recites the limitation that specific IgE binding to the derivative is 50% or less compared to the IgE binding to the naturally occurring allergen. Applicant discloses that the trimer of Bet v 1 was made as described in the prior art, and the indicated prior art document discloses that the trimer does not demonstrate a reduction in its specific IgE binding capacity (of record as reference L on the IDS received June 6, 2002, see entire document, particularly the right column of page 218, and also see lines 21-21 of page 13 of Valenta et al., WO 99/16467). As such a trimer of Bet v 1 does not show a diminution in specific IgE binding, and the specification does not appear to provide guidance or a working example concerning how to make a trimer of Bet v 1 that comprises this recited functional property. It should be noted that the specification does demonstrate that the trimer, when administered to experimental animal, did not elicit a significant IgE response that was directed to Bet v 1 (see particularly example 2 beginning on page 9 of the specification). The specification defines allergenic activity as the capacity to induce an IgE antibody response upon administration of a derivative to a test animal (see particularly page 4), and as such the Bet v 1 trimer has the functional property of reduced allergenic activity but does not have the recited property of a diminished capacity to bind preexisting allergen specific IgE as compared to the wildtype allergen.

As discussed above, the Bet v 1 trimer does not comprise all of the recited functional properties, but the polypeptides consisting of amino acids 1-73 or 74-159 of Bet v 1 do comprise these activities as is evidenced by Vrtala et al. since they failed to bind IgE antibodies and induced blocking antibodies following their administration to a subject (J. Immunol., 2000, 165:6653-6659, see entire document, particularly the abstract).

However, there currently is no art recognized method to distinguish allergic from non-allergic molecules (such derivatives comprising fragments and oligomers of allergens that do not bind IgE) on an a priori structural basis (Blumenthal et al. in Allergens and Allergen Immunotherapy, 3rd edition, 2004, pages

37-50, see entire document, particularly the last sentence of the third complete paragraph of page 39). If the identity of the IgE binding epitopes in an allergen are precisely known, it is not predictable as to which amino acid positions within an epitope need to be altered by site directed mutagenesis such that IgE binding is abrogated (Burks et al., Eur. J. Biochem., 1997, 245:334-339, see entire document, particularly the top right column of page 338). Even when a precise amino acid within in the epitope to be altered is identified, the choice of what that amino acid should be mutated to by site directed mutagenesis is not predictable since some substituted amino acids reduce IgE binding while others have no effect or unexpectedly increase IgE binding (Nishiyama et al., US Patent 6,187,311, see entire document, particularly lines 4-30 of column 3, and Reese et al., J. Immunol., 2005, 175:8354-8364, see entire document, particularly the paragraph that spans pages 8357 and 8358, Table I and Figure 2). The specification does not appear to teach what changes are to be made naturally occurring allergens to make derivatives that satisfy the recited functional criteria, and the teachings of the art indicate that the structure of the material obtained as an immunotherapeutic agent at the conclusion of the screening protocol cannot be predicted. Given the above, it appears that a skilled artisan would need to rely on trial and error to identify derivatives suitable for use in the recited method, and since the claims are broad in that except for claims 46, 51, and 52 the naturally occurring antigen is a member of a genus of allergens encompassing a very large number of members (see particularly chapter 11 of Lockey et al.) an undue amount of research would be required to practice the full breadth of applicant's claimed method.

Therefore, given that the claim recites the administration of agents derived from grass pollen allergens to treat all IgE-mediated disorders of any antigen specificity rather than those disorders that are specifically mediated by grass pollen specific IgE, the fact that an ongoing immune response, such as an IgE mediated disorder, cannot be effectively prevented since it has already occurred, the fact that applicant's example comprising a Bet v 1 trimer does not have all of the recited functional properties, and the difficulty of making the breath of claimed derivatives given the teachings of the specification and the art recognized difficulty in correlating the structural and functional properties of allergen derivatives, a skilled artisan would be unable to practice the full breadth of applicant's claimed invention without conducting an undue amount of additional research.

Applicant's arguments filed September 20, 2006 have been fully considered but they are not persuasive. Applicant's first argument is that the breadth of the claims are not directed to "IgE mediated disorders" but are limited to "the treatment of IgE mediated allergic disorders induced as a result of exposure to the major allergens of alder, hazel and birch".

This argument is not convincing because applicant is arguing limitations not claimed. The preamble of claim 33 broadly recites "IgE-mediated allergic disorders". While the claim does recite "the major allergens of alder, hazel and birch" the claim does not recite that the method is to only be used in treating alder, hazel and birch allergy patients.

Applicant also argues that the specification enables "prevention" of allergic disorders since therapy can begin prior to sensitization.

This argument is not persuasive since as discussed in the rejection of record, it cannot be predicted who will or will not develop an "allergic disorder". Is the entire human population to be treated by applicant's method? This problem is compounded

by the number of "allergic disorders" encompassed by the claims (which are not limited to birch, hazel and alder allergy) and the unreasonableness that the allergens of birch, alder and hazel (or their derivatives) can be successfully to treat, let alone prevent, the broad genus of all IgE-mediated allergic disorders. Further, given that the broadest reasonable interpretation of prevention encompasses 100% efficacy in 100% of patients and the art of Lockey (of record) teaches that due to the complex interplay of environmental and genetic factors it is not predictable who will or will not develop an allergic response to a given allergen, applicant's arguments are not persuasive that methods of prevention are enabled.

Applicant also argues that Bet v 1 trimers do comprise a diminished capacity to bind IgE due to the presence of IgE blocking antibodies in vivo.

This argument is not persuasive. Valenta et al., WO 99/16467 teach that a trimer of Bet v 1 does not differ from the wild type allergen in its capacity to bind IgE as discussed in the rejection of record. Blocking antibodies may sterically interfere with the ability of IgE and Bet v 1 trimers to interact, but the presence (or absence) of blocking antibodies does not change the intrinsic binding affinity between IgE and the allergen.

Applicant's final argument is that the specification provides adequate guidance and direction to make and use the "derivatives" recited in the instant claims.

This argument is not convincing because the only methodology disclosed for making "derivatives" involves random trial and error. Trial and error is inherently unpredictable and as such the specification does not provide guidance but it does provide an invitation for a skilled artisan to conduct additional research prior to making and using applicant's claimed invention. The requirement for a skilled artisan to conduct unpredictable research prior to making and using the full breadth of applicant's claimed invention indicates that the specification does not contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 33, 34, 37-41, 43-46, and 48-52 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The office action mailed June 20, 2006 states:

> Applicant has claimed a method of treating or preventing IgE-mediated allergic disorders by repeatedly administering an agent to a patient, wherein the agent is a derivative of a naturally occurring allergen that has been selected via a screening protocol to identify derivatives that induce a blocking antibody response and that exhibit decreased allergen specific IgE binding as compared to the wildtype allergen. In support of the genus of administered agents that are allergen derivatives, applicant has provided three examples concerning the birch pollen allergen Bet v 1, namely a trimer of Bet v 1, the polypeptide consisting of amino acids 1-73 of Bet V 1 or the polypeptide consisting of amino acids 74-159 of Bet v 1. This disclosure does not support the claimed genus for the reasons set forth below.
>
> The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).
>
> As discussed at length in paragraph 8 of this office action, the disclosed trimer of Bet v 1 does not comprise all of the recited functional properties, and as such it is not part of the recited genus of allergen derivatives. The two fragments of Bet v 1 do comprise all of the functional properties, but the independent claim is not limited to these particular fragments, or even to the birch pollen allergen Bet v 1. The recited genus of grass pollen allergens is very large and structurally diverse (see particularly chapter 11 of Lockey et al.), and applicant has defined derivatives in the paragraph spanning pages 2 and 3 of the specification to be fragments, oligomers, and chemically modified forms of naturally occurring allergens as well as molecules obtained by site directed mutagenesis of an allergen protein. The structure of these derivatives is not taught, and while functional properties are recited, the specification does not teach how these functional properties are correlated with structure. Further, the art teaches that correlations between structure and IgE binding (or the lack of IgE binding) cannot be predicted on an a priori structural basis (Blumenthal et al. in Allergens and Allergen Immunotherapy, 3rd edition, 2004, pages 37-50, see entire document, particularly the last sentence of the third complete paragraph of page 39). As such, the disclosure of the polypeptides consisting of amino acids 1-73 and consisting of amino acids 74-159 of Bet v 1 do not comprise a representative number of species to support the recited genus of grass pollen allergen derivatives, and thus the recited genus lacks written description.

Applicant's arguments filed September 20, 2006 have been fully considered but they are not persuasive. Applicant argues that the specification does provide written description for derivatives of the wild type allergens of alder, hazel and birch because all of these "derivatives" have the functional property of eliciting IgE-blocking antibodies and that "this identifying characteristic, without more, has given possession to the applicants, as of the filing date" the instant claimed methods.

This argument is not persuasive. As previously stated:

> The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

As discussed in the prior office action, the specification does not disclose a representative number of species that comprise the genus of derivatives of all birch, hazel and alder allergens, nor does it disclose a structure common to said derivatives. The disclosure of a functional characteristic, namely eliciting IgE-blocking antibodies, is made without a disclosed correlation between this functional characteristic and structure. As such, in the absence of more, applicant was not in possession of the genus of allergen derivatives recited for use in the instant claimed methods at the time the instant application was filed.

Note that in The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court held that disclosure of a single member of a genus (rat insulin) did not provide adequate written support for the claimed genus (all mammalian insulins), and that the genus of all mammalian insulins is more structurally similar than the genus comprising all derivatives of all allergens of birch, hazel and alder. In this same case the court stated "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene ("derivative") does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes ("derivatives") may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than

outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

Therefore, it appears that the broad genus of allergen derivatives recited in the instant method claims lacks adequate written description because there does not appear to be any correlation between structure and function excepting the working examples concerning the two fragments of Bet v 1 disclosed in the specification as having been made by Vrtala et al. in their 1997 J. Clin. Invest. paper. As such a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of allergen derivatives at the time the instant application was filed.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 33, 34, 37-40, 43-46, 48, 49 and 51 stand rejected and new claims 53 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659, see entire document) for the reasons of record.

The office action mailed June 20, 2006 states:

> Vrtala et al. teach a method of treating allergy by administering derivatives of Bet v 1 that induce the production of IgE-blocking antibodies and that are not bound by IgE antibodies that are specific for wildtype Bet v 1 (see entire document, particularly the abstract). The derivatives of Bet v 1 were repeatedly

administered to mice and rabbits at intervals of greater than 14 days. Mice were immunized four times, each dose comprising 5 μg of the derivatives adsorbed onto complete Freund's adjuvant (CFA), while rabbits were immunized three times, with each dose comprising 200 μg adsorbed onto CFA (see particularly the section *Immunization of mice and rabbits and measurements of mouse IgG subclass responses* in the right column of page 6654). The instant claims do not recite that the intended patient population consists of humans, and the specification teaches in the middle of page 2 that the disclosed methods of treatment are applicable to both humans and animals. As such, CFA is a pharmaceutically acceptable adsorbate for animals such as mice and rabbits.

Therefore, the prior art anticipates the claimed invention.

Applicant's arguments filed September 20, 2006 have been fully considered but they are not persuasive. Applicant's first argument is that the rejection of record is not a proper rejection under 102(b) since applicants have claimed priority to a European patent application filed on December 28, 2000 and as such the paper by Vrtala et al. is not prior art.

The effective US filing date for the instant application, i.e. 10/026,931, is December 27, 2001. Applicant has claimed foreign priority to a European document filed on December 28, 2000. Section 706 of the MPEP teaches:

> V. DETERMINING THE EFFECTIVE FILING DATE OF THE APPLICATION
> The effective filing date of a U.S. application may be determined as follows:
> (A) If the application is a continuation or divisional of one or more earlier U.S. applications or international applications and if the requirements of 35 U.S.C. 120 and 365(c), respectively, have been satisfied, the effective filing date is the same as the earliest filing date in the line of continuation or divisional applications.
> (B) If the application is a continuation-in-part of an earlier U.S. application or international application, any claims in the new application not supported by the specification and claims of the parent application have an effective filing date equal to the filing date of the new application. Any claims which are fully supported under 35 U.S.C. 112 by the earlier parent application have the effective filing date of that earlier parent application.
> (C) **If the application claims foreign priority under 35 U.S.C. 119(a)-(d) or 365(a)>or (b)<, the effective filing date is the filing date of the U.S. application**, unless situation (A) or (B) as set forth above applies. The filing date of the foreign priority document is not the effective filing date, although the filing date of the foreign priority document may be used to overcome certain references. See MPEP § 706.02(b) and § 2136.05.

Vrtala et al. published their paper more than one year before the effective US filing date of the instant invention. As such the reference is prior art under 35 USC 102(b).

Applicant's second argument is that "the Vrtala publication is at best a mere experimental disclosure of certain aspects of the present invention and does not enablingly disclose the invention as claimed". Applicant specifically argues that the claims are now limited to treating humans and that human treatment is not enabled by Vrtala et al. because the adjuvant used in the working example, i.e. complete Freund's adjuvant, is not pharmaceutically acceptable for use in humans.

This argument is not persuasive because the abstract and discussion section of the journal article identifies how the fragments of Bet v 1 made by Vrtala et al. can be used for clinically effective treatments of birch pollen allergy in settings such as specific immunotherapy (see particularly the last sentence of the abstract and the left column of page 6658). As such a skilled artisan would readily envisage applying the disclosed treatment methodology to humans, especially given that the teachings of Vrtala et al. are not limited to their specific working example.

Applicant's third argument is that claim 33 and its dependent claim have a "periodicity element" which is essential to successful immunotherapy and that "the Vrtala reference cannot reasonably be said to have sufficiently disclosed, to a patentably enabling detail, the periodicity element claimed in the invention which is very vital to a successful immunotherapy."

This argument is not persuasive because Vrtala et al. teach monthly injections, thus satisfying all recited periodicity elements of the indicated claims. Specifically, monthly injections mean that the "period between administrations is at least 14 days" and immunizations occurred 4 times (see particularly the right column of page 6654).

Note that newly presented claims 53 and 54 have been joined to the rejection. These new claims recite administering peptides consisting of amino acids 1-73 or 74-159 of Bet v 1. The specification indicates on page 8 that the recombinant Bet v 1 fragments used in the instant specification are the peptides disclosed in the 1997 J. Clin. Invest. article by Vrtala et al. In this 1997 article, Vrtala et al. teach how to make recombinant Bet v 1 fragments consisting of amino acids 1-74 and 75-160 of Bet v 1. Note that the 2000 J. Immunology paper by Vrtala et al. that forms the basis of this rejection discloses the use of Bet v 1 fragments consisting of amino acids 1-74 and 75-

160, and references the 1997 J. Clin. Invest. paper in the materials and methods section for details concerning the manufacture of said peptides. As such, it appears that the Bet v 1 fragments taught in the prior art and those used in the instant specification are the same fragments with the discrepancy between the amino acid numbering being a typographical error of the instant specification.

10. Claims 33, 34, 37, 46, and 48-51 stand rejected and new claims 53 and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Valenta et al. (WO 99/16467 A1, see entire document) as evidenced by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659, see entire document) for the reasons of record.
The office action mailed June 20, 2006 states:

> Valenta et al. teach a method of treating allergy by repeatedly administering derivatives of Bet v 1 (see entire document, particularly the abstract and the paragraph spanning pages 5 and 6). The Bet v 1 derivatives comprise the polypeptides consisting of amino acids 1-73 of Bet v 1 and amino acids 74-159 of Bet v 1 (see particularly lines 9-20 of page 4 and pages 15-19). These polypeptides are taught as being combined with the pharmaceutically acceptable adsorbate and adjuvant aluminum hydroxide prior to *in vivo* administration (see particularly lines 2-9 of page 6). These polypeptides do not bind IgE isolated from known birch pollen allergenic patients, and thus they comprise reduced IgE binding as compared to wildtype Bet v 1 allergen (see particularly the paragraph spanning pages 17 and 18). Valenta et al. did not demonstrate that these polypeptides, when administered to a subject, induce a blocking antibody response. However, it is inherent that such a response to the polypeptides administered by Valenta et al. occurs as evidenced by Vrtala et al., who teach that administration of the same polypeptides as taught by Valenta et al. induce a blocking antibody response (see entire document, particularly the abstract, discussion, and Tables II and III).
>
> Therefore, the prior art anticipates the instant invention.

Applicant's arguments filed September 20, 2006 have been fully considered but they are not persuasive. Applicant argues that the art references are not enabling disclosed the periodicity element of claim 33 and its dependent claims.

This argument is not persuasive. The only "periodicity element" of the recited claims is found in claim 33 which recites "comprising periodically administering for a number of times...". In the paragraph spanning pages 5 and 6 of Valenta et al., teach:

> The second aspect of the invention is specific hyposensitization therapy. This therapy may be performed as known in the art for protein allergens and encompasses administering repeatedly to the mammal, typically a human individual, suffering from type I allergy against the protein allergen an immunogen that is capable of raising as IgG immune response against the protein allergen. Administration may be done systemically, for instance by

injection, infusion, etc., but also the oral route has been suggested in order to expose the intestinal part of the immune system. The immunogen may be admixed with suitable adjuvants such as aluminium oxide. See further Norman P S, "Current status of immunotherapy for allergies and anaphylactic reactions" Adv.Internal. Medicine 41 (1996)681 713.

How can an allergen be administered multiple times without said administration occurring over a period of time?

Further, new claims 53 and 54 have been joined to this rejection since Example 3 discloses that the Bet v 1 fragments used in the example are the fragments disclosed by Vrtala et al. in their 1997 J. Clin. Invest. paper, and as previously discussed it appears that the recitation of amino acids 1-73 and 74-159 in the instant specification is a typographical error since the instant specification teaches the '97 paper as the source of the peptides used in the examples of the instant specification and the '97 reference clear teaches fragments 1-74 and 75-160 of Bet v 1 rather than fragments 1-73 and 74-159 of Bet v 1.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 33, 49, and 50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659, see

entire document) in view of Hem et al. (chapter 9 of Vaccine Design: The Subunit and Adjuvant Approach, 1995, pages 249-76, see entire document) for the reasons of record.

The office action mailed June 20, 2006 states:

> The teachings of Vrtala et al. have been discussed above. While Vrtala et al. teach that their allergen derivatives are to be used in methods of human administration (see entire document, particularly the abstract and discussion sections), these teachings differ from the instant claimed invention in that they do not teach the use of aluminum hydroxide as part of the administered composition.
>
> Hem et al. teach that aluminum hydroxide is a widely used adjuvant that offers the important advantage of being the only adjuvant licensed by the food and Drug Administration for administration to human patients (see entire document, particularly the introduction).
>
> Therefore, it would have been obvious at the time the invention was made to substitute aluminum hydroxide for the CFA used in the methods of administration taught by Vrtala et al. Motivation to make this substitution comes from the teachings of Vrtala et al. that their allergen derivative compositions are to be administered to humans and the teachings of Hem et al. that the only adjuvant that can be administered to human patients is aluminum hydroxide.

Applicant's arguments filed September 20, 2006 have been fully considered but they are not persuasive. Applicant argues that the recited periodicity element is not taught in any of the indicated references.

This argument is not persuasive and has been adequately addressed above.

13. Claims 33, 38, and 41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659, see entire document) for the reasons of record.

The office action mailed June 20, 2006 states:

> The teachings of Vrtala et al. have been discussed above. These teachings differ from the instant claimed method in that while Vrtala et al. teach repeated administration of allergen derivatives wherein the period between administrations is at least 14 days, Vrtala et al. do not teach that the time interval between the third and fourth administrations is longer than the time interval between the first three administrations. However, it would have been obvious to a person of ordinary skill in the art at the time the invention was made modify the interval between administrations. As person of ordinary skill in the art at the time the invention was made would have been motivated modify the time intervals to optimize the treatment method, and determining the optimal intervals of administration of the allergen derivative is well within the purview of one of ordinary skill in the art at the time the invention was made. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). See MPEP § 2144.05 part II A.

Applicant's arguments filed September 20, 2006 have been fully considered but they are not persuasive. Applicant argues that the examiner has engaged in hindsight reasoning to reject the claims.

This argument is not persuasive. Vrtala et al. disclose that a blocking antibody response can be obtained in a patient subsequent to monthly administrations of their Bet v 1 fragments. As such, the general conditions of the claims (i.e. periodic administration wherein the period between administrations is greater than 14 days) are taught in the art and *In re Aller* held that when such general conditions are known, optimizing involves only routine skill in the art. Applicant states in the reply that only routine skill is involved ("Applicants understand that a simple and elegant screening procedure of this invention involves routine skill in the art...") but then states that the exact timing and dosages are not obvious. As stated in the rejection of record, a skilled artisan would be motivated to optimize the protocol of Vrtala et al., and given that such optimization is routine and thus within the skill of an ordinary artisan, the claimed method is obvious.

The following are new grounds of rejection necessitated by applicant's claim amendments received September 20, 2006.

14. Claims 53 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, these claims recite specific length fragments of Bet v 1, yet the specification does not provide a sequence for Bet v 1. Many Bet v 1 sequences are known in the art, and these sequences differ in amino acid composition and length (Friedl-Hajek et al., Molecular Immunology, 1999, 36:639-645, see entire document particularly Figure 1). As such, defining a fragment of Bet v 1 as being, for example, amino acids 1-73, without recitation of a single specific reference sequence for Bet v 1 renders the claim indefinite since the metes and bounds of the administered allergen derivatives are not clear.

15. No claims are allowable.

16. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Patent Examiner
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November 16, 2006

11/2/06

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER